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June 10, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Dear Dockets Management Branch Staff:

RE: Docket No. 02D-0094

Please find enclosed the comments of the Cancer Therapy Evaluation Program of the National Cancer Institute concerning Docket No. 02D-0094 entitled *Draft Guidance for Industry on IND Exemptions for Studies of Lawfully Marketed Cancer Drug or Biologic Products* published in the Federal Register on April 9, 2002.

Please contact me at the number above or by e-mail (shoemakerd@ctep.nci.nih.gov) if you have any questions concerning our comments.

Sincerely yours,

Dale Shoemaker

Dale Shoemaker, Ph.D.
Chief, Regulatory Affairs Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
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Enclosure 02D-0094

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cc: Dr. Christian
Dr. Grochow
Dr. Kaplan

IND EXEMPTIONS FOR STUDIES WITH MARKETED CANCER AGENTS

The following are general comments relating to the FDA draft Guidance on IND exemptions for studies of marketed cancer drugs or biological products:

- Implementation of Section V.B. of the draft Guidance (Studies That Generally Are Not Exempt, page 6) would likely lead to a larger proportion of CTEP-sponsored (funded) trials (especially phase 3 studies) requiring INDs. This will further increase the growing burden of regulatory requirements for investigators and for the clinical research community. This would have serious resource implications and could lead to a reduction in the number of trials conducted.

- Publication of this Guidance will lead to the presumption that INDs are required for studies that involve the use of a marketed agent as adjuvant chemotherapy and for studies that involve the substitution of a new agent of unproven activity when standard therapy provides cure or increased survival. As investigators (and IRBs) implement this Guidance, there could be a substantially larger number of studies conducted under IND. For childhood cancers, a setting in which curative therapy is available for most diagnoses and for which phase 3 trials often compare a standard regimen to a regimen that incorporates a marketed cancer agent, most phase 3 studies would require an IND.

- A study that **may** eventually be used to support approval of a new indication does not mean it was **intended** to support the approval. Many CTEP-sponsored phase 3 studies could lead to a change in labeling, even though this may not have been the intent of the study investigators who designed and conducted the study.

- CTEP often sponsors "proof of principle" clinical trials. Studies designed to address a specific principle may not be appropriate for isolating the contribution of a specific agent. There should be no *a priori* assumption that studies designed to isolate the contribution of a specific agent and that are therefore suitable for a licensing indication are to be preferred over studies that address important scientific or clinical questions but do not isolate the contribution of a single agent.

- Concerns about the impact of the draft Guidance are diminished when a pharmaceutical sponsor has planned and will support a study for a new indication and/or significant change in the labeling. However, companies may often be unwilling to sponsor the IND and would expect CTEP or the Cooperative Groups (or individual investigators) to do so.

- Regardless of the eventual wording of this Guidance, CTEP would be interested in exploring proposals to streamline the regulatory processes associated with clinical trials requiring INDs, especially for phase 3 studies (e.g., streamlining the submission process and the required reporting following IND activation including Annual Reports and adverse event reporting).

The following are specific questions concerning the draft Guidance:

- What is the added protection for research subjects by conducting the phase 3 studies described in Section V.B. under an IND as opposed to other methods [e.g., review by CTEP, IRBs, DSMBs] already in place for protecting research subjects?

- What is considered acceptable therapy for specific cancers using marketed agents in regimens that themselves may or may not be licensed for these tumor types? Should an investigator rely on publications of the safe use of these regimens? Does labeling control what is the standard therapy?

- Section IV.B. recognizes that investigators and their IRBs are able to determine based on the scientific literature and generally known clinical experience whether there is a significant increase in risk associated with the use of an agent for studies involving a new use, dose, schedule, route of administration, or new combination of marketed cancer products. If investigators and IRBs are able to make this risk determination, then why are they not considered able to determine whether there is significantly increased risk for studies involving adjuvant therapy and for studies involving substitution of a new agent in settings were standard therapy provides cure or increase in survival?

- If investigators and their IRBs have determined that there is no significant increase in risk associated with the use of an agent (i.e., the risk-to-benefit ratio for the experimental therapy is acceptable) and if a pharmaceutical company is reluctant to sponsor an IND and no supplemental application is anticipated, then what is the standing of the FDA to require an IND for studies involving adjuvant therapy and for studies involving substitution of a new agent in settings where standard therapy provides cure or increase in survival?

- Concerning study of new combinations (Section V.A.3, page 6), it is not clear whether "described in the literature" refers to preclinical or clinical studies. In addition, it would be helpful to better define "incremental differences in doses".

- Are there ways to streamline regulatory processes associated with clinical trials requiring INDs, especially for phase 3 studies of marketed cancer drugs or biological products?